Immunity
Commentary

Specialized Perinodal Fat Fuels and Fashions Immunity

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Adipose tissue around lymph nodes is usually removed prior to the study of immune activity—but is it time to reconsider this practice? Perinodal adipose tissue may provide not only a specific lipid resource but also fatty acids, dendritic cells, and soluble mediators that modulate local immunity.

Dietary fats influence immunity—but how are these effects targeted to the immune system, and how is immune activity buffered from the immediate effects of current dietary components? Perinodal adipose tissue (PAT) is in the form of small depots or regions of larger depots of stored fat in which lymph nodes are embedded and is a unique and conserved feature of mammalian anatomy. The specialized properties of this PAT provide a local resource that interacts with the lymph node and appears to form a buffer of stored adipose tissue dedicated to the functioning of the lymph node. There is increasing evidence that adipose tissues do not merely provide an energy resource but are also specialized to contribute to local physiological mechanisms. To this purpose, they are not homogeneous but show site-specific properties. One example of site-specific specialization of white adipose tissue is that of pericardial fat, which is highly adapted as a local energy resource with its small adipocyte size, high rates of fatty-acid incorporation and synthesis, and insulin-induced fatty-acid breakdown (Rabkin, 2007). Another example of this specialization is seen in the close physiological relationship between adipose tissue surrounding breast cancer and the tumor itself, with evidence of endocrine and paracrine mechanisms that connect adiposity and breast cancer (Schaffler et al., 2007). However, the most detailed evidence for major adaptation and site-specific properties in normal white adipose tissues is described for PAT. Indeed, the specialized properties of PAT mean that this tissue not only acts as a dedicated lipid resource fueling immune activation in lymph nodes but also provides key fatty-acid, cellular, and adipokine immunoregulatory materials that support and regulate local immunity (Figure 1). Conversely, antigenic stimulation and activity of cells of the immune system may influence adiposity. Here I highlight a few examples of the close interaction between PAT and local lymph nodes and its effects on immune responses.

Specialized Fatty-Acid Content in PAT

The nature of the fatty-acid content of PAT is one aspect showing site-specific specialization. In humans, PAT has a substantially higher content of polyunsaturated fatty acids (PUFAs) than adipose tissue distal from the node, including the subcutaneous tissues (Westcott et al., 2005). A similar distribution of fatty acids occurs in rodents, in which PUFA-rich fats, released by lipolysis from triacylglycerols in PAT, appear to be taken up into lymph nodes and are incorporated in lymphoid cells after immune stimulation. There is a two-way interaction between PAT and the lymphoid tissue it encircles. Activated lymphocytes can promote glycerol release from PAT but have little effect on adipocytes from other sites. Conversely, PAT, but not adipose tissue from other sources, is able to reduce lymphocyte proliferation in vitro (Pond [2003] for references). The immunomodulatory effects of PUFAs are well described, with omega 3 and omega 6 PUFAs and their metabolic products often being immunosuppressive although, in some instances, omega 6 PUFAs may potentiate immunity. Possible mechanisms of action of PUFAs or their metabolites on the immune system include modulation of cellular-membrane fluidity and raft formation, signal transduction, and/or gene expression, affecting functions such as antigen presentation and cell migration (Sijben and Calder [2007] for references).

Site-specific changes of fatty acids within PAT are likely to have a major impact on the local immune system. Crohn's disease, an inflammatory disease of the gut, possibly resulting from an abnormal response to gut microbiota, is characterized by hypertrophy of mesenteric adipose tissue. A feature of this disease is the absence of selective accumulation of PUFAs in PAT and of the correlation between fatty-acid content of PAT and lymph node cells (Westcott et al., 2005). These changes suggest that the normal immunomodulatory nature of fatty acids stored in PAT can be lost in inflammatory disease.

Soluble Mediators and PAT

A second and related specialization of PAT is its sensitivity to and production of cytokines. The general relationships between cytokines or adipokines within adipose tissues and the immune system have been extensively discussed (Hasenkrug, 2007; Tilg and Moschen, 2006). However, PAT is exquisitely equipped for local interactions with lymphoid tissues. For example, cytokines such as tumor necrosis factor-α and interleukin-6 (IL-6), to both of which PAT is especially responsive, are key modulators in the development of immunity, can promote migration of dendritic cells (DCs) into lymph nodes, and are involved in responses to bacterial antigens, particularly during early stages of immune responses (Hasenkrug, 2007; Tilg and Moschen, 2006). These cytokines have minimal effects on lipolysis of perirenal or gonadal

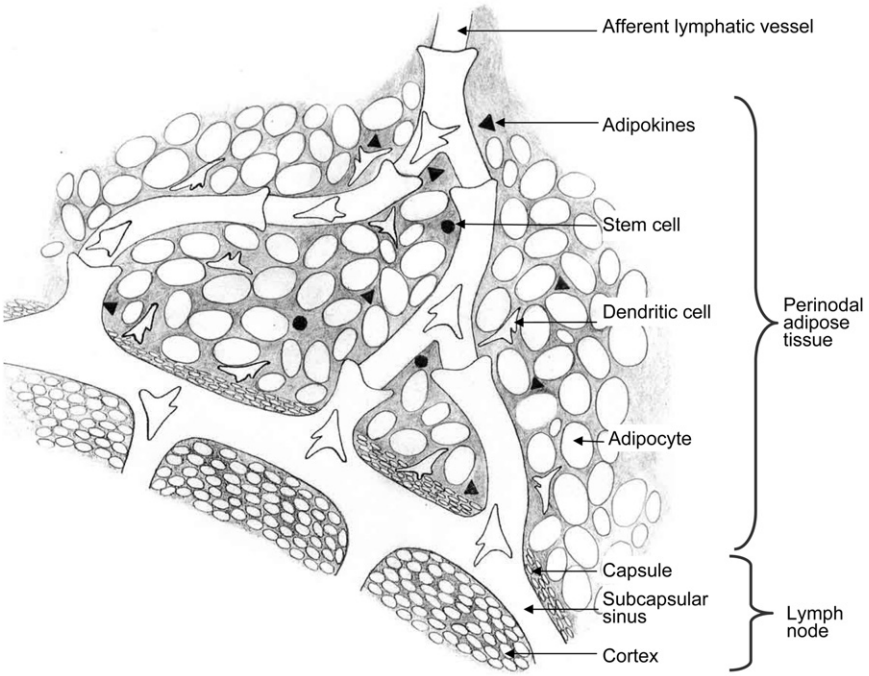

Figure 1. Perinodal Adipose Tissue Is Specialized to Provide Fatty Acids, Adipokines, and Dendritic Cells that May Influence Local Immune Responses

PAT is higher in polyunsaturated fatty acids than adipose tissue distal from nodes and may downregulate lymphocyte activation. PAT also contains adipokines that may influence immune activity. Afferent lymphatic vessels enter PAT and divide before entering through the lymph node capsule into the subcapsular sinus of the lymph node. Dendritic cells (DCs) enter lymph nodes via afferent lymph and are found in abundance in PAT but are not present in adipose tissue distal from the lymph node or in subcutaneous adipose tissue.

adipocytes in vitro but stimulate glycerol release from PAT (Pond, 2003), which may thus provide a resource to support local immune activity. However, when IL-4 is also present, glycerol release is suppressed, particularly in PAT, so that alterations in local cytokines together with related variations in sensitivity of PAT adipocytes may combine to produce changes in local immune activity (Pond, 2003). IL-4 can also prevent synthesis of prostaglandin E2 (PG E2) from its fatty-acid precursors but can induce expression of PPAR-γ (a key regulator of adipocyte differentiation and lipid metabolism) and promote the oxygenation of free PUFAs, which generates PPAR-γ ligands. These effects are likely to reduce DC maturation and activity because PGE2 can promote DC differentiation and maturation whereas PPAR-γ may be anti-inflammatory, blocking DC maturation (Thurnher, 2007). Such effects are particularly relevant to PAT because PAT and not adipose tissue from elsewhere contains DCs (see below). PAT adipocytes are also more sensitive to noradrenalin, and their maximum rate of lipolysis is higher than those at other sites (Pond, 2003). Adipokines produced specifically within adipose tissues also affect immune stimulation. For example, adiponectin generally has immunoregulatory properties, whereas leptin, in addition to its role in energy homeostasis, can act as a proinflammatory cytokine.(Hasenkrug, 2007; Tilg and Moschen, 2006). Thus, cytokines, in concert with the local fatty-acid milieu, may modulate inflammation in part by effects on maturation and function of DCs.

Immune Cells in PAT

A third specialization found in normal PAT is the presence of high numbers of DCs. The presence of DCs is a particular property of adipose tissue containing lymphoid structures and can be modulated by antigenic stimulation, diet, and disease. Omentum is the adipose tissue associated with the spleen in mice and is a larger organ in humans, hanging like an apron in the abdomen and containing embedded pockets of lymphoid cells. Omental tissue in humans contains large numbers of DCs identified by morphology, phenotype, and stimulatory function, whereas normal subcutaneous fat contains virtually no DC (Bedford et al., 2006). In rodents, putative DCs are also found in PAT, but, again, few are found in fat distal from the nodes or in subcutaneous fat. The presence of these large mononuclear cells increases on antigenic stimulation, and their numbers are moderated by the presence of a diet high in omega 3 fatty acids (Mattacks et al., 2004). In addition to the DCs, there are stem cells present in PAT (Bedford et al., 2006), as widely reported for other adipose tissue depots. Preadipocytes also have the potential to develop into macrophages (Charriere et al., 2003). Indeed, there is increasing evidence for involvement of adipose tissue macrophages in obesity-related inflammation (Weisberg et al., 2003; Wellen and Hotamisligil, 2003). DCs in adipose tissue can also change in disease, as exemplified by those in the omentum from patients with Crohn's disease; in addition to the reduction of stored PUFAs in PAT already described, the numbers of bone-marrow-derived cells from omentum in Crohn's disease is increased 5-fold. Substantial numbers of granulocytes, not seen in control PAT, are present, but a high proportion of the cells have a DC morphology and phenotype. These cells express increased amounts of costimulatory molecules, suggesting innate activation of DCs in Crohn's disease, although MHC class II and stimulatory function for T cells are lost (Bedford et al., 2006). These changes suggest that DCs from PAT may contribute to or reflect changes in local immune activity in inflammatory disease. DCs can take up large amounts of lipid on stimulation (Maroof et al., 2005) and may provide a major route via which fatty acids and their metabolic products stored in PAT both provision and exert their immunoregulatory properties within the lymph node.

Adipose Tissue and Responses to Antigens

The provision of a local lipid resource that supports immune activity appears to have evolved coordinately with recognition structures for responses to antigenic stimulation; clearly, recognition of antigenic differences is impotent without resources to provision an immune response. Where

fatty acids or their metabolites can also cause immunomodulation, such resources are likely to evolve in concert with immune recognition to be utilized for the benefit of either the host or an invading organism. This concept is supported by the evidence that genes involved in the immune system, in nutrition, and in the function of adipose tissue have been subject to recent selection in human populations (Voight et al., 2006). Thus, many receptors for antigens on myeloid cells interact with lipids or their metabolites, an interaction that may influence both immune activity and lipid homeostasis. One example of direct effects of fatty acids is seen in the modulation they cause via receptors for bacterial antigens, the Toll-like receptors (TLRs). Signaling through TLRs induces in DCs innate immune responses that in turn link to adaptive immune responses. Saturated fatty acids may promote activation via TLRs, whereas *n-3* PUFAs inhibit agonist-induced TLR activation, suggesting that differential modulation of immune responses occurs. Indeed, the saturated fatty acid, lauric acid, upregulates the expression of costimulatory molecules (CD40, CD80, and CD86), MHC class II, and cytokines (IL-12p70 and IL-6) in bone-marrow-derived DCs via TLR activation. This activation produces increases in the capacity to stimulate T cells (Weatherill et al., 2005). In contrast, the *n-3* polyunsaturated fatty acid, docosahexaenoic acid, normally more abundant in PAT than in other adipose tissues, inhibits the TLR4-agonist-induced upregulation (Thurnher, 2007). The activation of TLR4 signaling in adipocytes and macrophages by nutritional fatty acids is confirmed in mice from the blunting of inflammatory signals they induce in the absence of TLR4 (Shi et al., 2006). The relatively high amounts of PUFAs normally in PAT would tend to downregulate signaling through TLRs. In the PAT of subjects with Crohn's disease, there are increases in the proportion of saturated fats, including palmitic acid, which can also promote TLR-induced activation in DC (Lee et al., 2001; Westcott et al., 2005). This increase in saturated fatty acids is likely to combine with the presence of a proinflammatory microbiota to promote local inflammatory activity in this disease. Increased IL-6 also would promote lipolysis of local adipocytes, thereby releasing glycerol for utilization as an energy substrate. Dietary fatty acids and those stored around lymph nodes may, therefore, play a seminal role in differential modulation of local immune activity and alter the effects induced by exogenous and endogenous antigens. Dietary PUFAs and their longer-term effects on changes in the fatty acids stored around lymph nodes are, thus, likely to be implicated in susceptibility to and activity of many chronic diseases via effects acting locally through antigen receptors such as the TLRs.

Some effects of PUFAs may be less direct and are mediated by metabolic products of the fatty acids that share receptors with antigens. The activities of prostaglandins and leukotrienes have been widely reported and have effects on the maturation and function of DC. Many lipids or their metabolites also affect the migration of lymphocytes and DC, and these include PGE2, leukotrieneC4, and sphigosine-1-phsophate (Thurnher, 2007). Resolvins represent a more recently described category of fatty-acid-derived immune modulators that can interact with a receptor for antigen on DC and may also influence the migratory properties of the DCs. ChemR23 is a G protein-coupled receptor expressed on DCs, particularly those of the $CD11c^-$ (plasmacytoid) subset (Zabel et al., 2005). This molecule is a coreceptor for human and simian immunodeficiency virus (Martensson et al., 2006). Two major innate ligands for this receptor have been identified. The first is the *RARRES2* gene product, chemerin, expressed as an inactive protein precursor, which is activated in situ at sites of inflammation. In vitro, chemerin stimulates $ChemR23^+$ dendritic cells to migrate across epithelial cell layers. The second ligand for ChemR23 is Resolvin E1 and is derived from omega 3 PUFAs, which are found in increased quantities in PAT. Resolvin E1 blocks migration of DC to chemerin. Early in vivo experiments involving animal models of inflammatory disease, such as inflammatory bowel disease, imply a therapeutic role for resolvin E1 in improving outcome (Arita et al., 2005). This unique chemotactic axis provides an added explanation for the benefit and therapeutic role of omega 3 polyunsaturated fatty acids and their derivatives such as resolvinE1. Conversely, the link with human and simian immunodeficiency virus indicates that ChemR23 is a "minor receptor," but retrovirally induced blocking of DC migration has been reported in animal models of HIV infection (Gabrilovich et al., 1994), and one can question whether this receptor sharing might provide a mechanism by which the virus could block a normal migration pathway of DC.

Effects of Antigenic Stimulation on Local Adiposity

The examples of coordinate evolution of antigen receptors and receptors for fatty acids and their derivatives so far outlined have concentrated on the possible implications for the functioning of the immune system. However, the other side of this equation is the reciprocal effects that antigenic stimulation may have on adiposity and energy homeostasis. Exposure to some bacterial antigens, such as endotoxin, or viral antigens, including those of adenoviruses, can promote obesity (Cani et al., 2007; Tsukumo et al., 2007; Wellen and Hotamisligil, 2003; Whigham et al., 2006), providing support for two-way interactions between immune activation and adipose tissue. An example that may relate directly to the shared receptor for antigen and fatty acid, TLR4, is the observation that diet-induced obesity can be associated with LPS stimulation and is moderated in TLR4-deficient mice (Cani et al., 2007; Tsukumo et al., 2007). Other changes in adiposity link specifically to the specialized function of PAT, e.g., lipodystrophy that occurs in some HIV patients on treatment with proteinase inhibitors, and hypertrophy of PAT in rodents during prolonged mild antigenic stimulation (Pond, 2003). It is these PAT depots that become enlarged in the HIV-positive patients, with or without atrophy of non-PAT depots. Retroviral infection is known to make DCs alter their secretion of some of the cytokines to which perinodal adipocytes respond (Pond, 2003). Thus, the proposed relationship between adipose tissue and the immune system can also be used to explain the redistribution and hypertrophy of adipose tissue that takes place after a long period of chronic inflammation such as that which characterizes the mesenteric adipose tissues in Crohn's disease and PAT in HIV infection.

Conclusions and Perspectives

PAT is a preserved feature of mammals. It has site-specific properties adapted to allow contributions of stored fatty acids,

produces and responds to local cytokines, and contains large numbers of antigen-presenting dendritic cells. All of these factors have the potential to influence local immunity. For immunologists studying the immune activity of the lymph nodes, removal of PAT may avoid the release of fats that make cell handling problematic. However, although this maneuver undoubtedly has helpful technical consequences, it may mean that a major, integrated part of the immune system is lost. PAT is clearly not just a load of inconvenient lard but is also a fully active partner to the lymph node, resourcing and regulating immunity. Exciting questions emerge from this new perspective. Changes in the properties of PAT in inflammatory bowel disease demonstrate the potential of perinodal adipose tissue to influence immune status and vice versa. However, to what extent do different antigens, infections, and immunological diseases contribute to variations in PAT composition? Diet, influenced by the gut microbiota, is obviously the ultimate resource for many lipids that influence immune activity. For dietary lipids to be utilized effectively, they have to reach the right location in PAT. What are the mechanisms that ensure that the right type of adipose tissue is stored in the perinodal area? What is the source of local DCs within adipose tissue? Finally, how are locally stored lipids and their products and adipokines taken up and utilized by the local cells of the immune system? Many receptors for antigens on myeloid cells, including those for bacterial and viral antigens, interact with lipids or their metabolites to influence local immune activity. Conversely, there is increasing evidence that antigenic stimulation and responsiveness can influence energy homeostasis and obesity. The coevolution of antigen recognition, the energy resource required to provision immune activation, and the immunomodulatory function of involved adipose tissue and its metabolites forms a natural integration of factors that are likely to contribute both to adiposity and to the optimal functioning of the local immune system. However, many of the details of these interactions remain tantalizingly vague.

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